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SPIE.

Event: European Conferences on Biomedical Optics, 2019, Munich, Germany

Optical coherence tomography controlled selective retina therapy with a novel microsecond laser

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ABSTRACT

Selective retina therapy (SRT) is a short pulse (µs-regime) alternative to conventional laser photocoagulation (LPC) for treatment of retinal diseases. LPC leads to collateral damage of retinal layers adjacent to the retinal pigment epithelium (RPE), including healthy, non-regenerative photoreceptors due to the high thermal load, whereas in SRT, RPE cells are destroyed by microbubbles without damaging the neuronal retina. A novel experimental SRT laser operating at 532 nm wavelength can deliver 2 – 20 µs pulse sequences. Its tight integration into an upgraded diagnostic SPECTRALIS system combines beam control for treatment planning with real-time optical coherence tomography (OCT) overexposure protection of the photoreceptors. This "Spectralis Centaurus" system, was built and preliminary tested on porcine ex-vivo samples, reaching an unprecedented accuracy with unique planning and follow-up capabilities for upcoming clinical cellular level micro-surgery. The combination of OCT with SRT selectively limits cell death to the RPE by precisely controlling energy deposition while optically monitoring tissue response.

Keywords: Selective retina therapy, Retinal pigment epithelium, (170.0170) Medical optics and biotechnology, (170.4500) Optical coherence tomography, (170.4460) Ophthalmic optics and devices, (170.3890) Medical optics instrumentation, (170.4470) Ophthalmology

1. INTRODUCTION

Whereas diabetic retinopathy with diabetic macular edema is the leading causes of blindness in the working-age population, age-related macular degeneration remains the major cause of severe vision loss of the elderly in industrialized countries[1,2,3,4]. Central serous chorioretinopathy is mostly transient but can cause permanent visual compromise in some patients. To treat these retinal diseases, which are associated with retinal pigment epithelium (RPE) dysfunction, conventional laser photocoagulation (LPC) techniques were shown to be effective[5,6]. Today, LPC still remains a widely used method, but due to the slow heating process and the strong heat dissipation into the surroundings, the use of long laser pulses in the millisecond-range or even continuous wave lasers application lead to collateral damage of surrounding components like Bruch's membrane, choriocapillaris and particularly, healthy overlying photoreceptor cells[7,8], which in turn leads to scotoma, reduced night vision, and disruption of the retinal anatomy from scarring[9,10]. These adverse effects have led to the development of new forms of laser treatments, whereas selective retina therapy (SRT) is particularly suitable since it selectively targets RPE cells without affecting the neighboring neural retina, choroid, and photoreceptors. The basis for this selective RPE damage are the strongly light-absorbing melanosomes inside RPE cells, where about 50% of the incident light in the green spectral range[11] is converted to heat. Due to the thermal confinement in SRT, ~1 microsecond long laser pulses cause heating of melanosomes to at least 150°C, which leads to vaporization of surrounding liquid and subsequent microbubble formation on the melanosome surface[12]. The consequence of this rapid expansion is partial or complete RPE cell disruption followed by RPE cell death, without severely affecting adjacent retinal layers[13]. This selective cell death is desired, since resulting lesions are substituted later on by expansion and proliferation of highly regenerative RPE cells[8]. This stimulation of RPE cell migration, local inflammation and replacement of old cells finally leads to improved metabolism at target sites without scarring[14]. The key challenge of photoreceptor-cell conserving therapy of the retina is the complexity of radiant exposure control due to inter- and intra-patient variability of tissue absorption.

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Medical Laser Applications and Laser-Tissue Interactions IX, edited by Lothar D. Lilge, Carsten M. Philipp, Proc. of SPIE Vol. 11079, 1107903 · © 2019 SPIE · CCC code: 1605-7422/19/$21 · doi: 10.1117/12.2526720

Since SRT suffers from the lack of real-time optical feedback and being undetectable during visual inspection of the fundus, the selective RPE damage caused by this therapy is practically and efficiently only retrospectively identified via fundus fluorescein angiography (FFA). However, FFA has two major drawbacks. It is medically invasive and second, it cannot be used as a real-time dosimetry tool. Besides other novel detection methods, like opto-acoustics, light reflection and small bandwith-interferometry, optical coherence tomography (OCT) can provide reliable dosimetry control for SRT. With its optical access, OCT can image the three-dimensional structure and comfortably discriminate the level of RPE lesions[13] indirectly as a change of signal strength[15]. This method was described by Steiner et al.[16,17,18,19]; effects of treatment laser pulses were indirectly detected as a change of intensity in axial OCT scans (A-scans), which correspond to the local reflectivity of tissue. Using signal changes of OCT M-scans, Kaufmann et al.[15,20] were able to precisely predict real-time retinal lesions during SRT. Furthermore, Kaufmann et al. showed, that SRT in ramp-mode combined with a fast algorithm-based OCT treatment stop allows reliable dosimetry during SRT. The system presented here implements these findings within a multimodal commercial-class platform with targeting clinical application and features a novel experimental SRT laser.

2. MATERIALS AND METHODS

The Spectralis Centaurus system (Figure 1, 2) was engineered and built by the HuCE optoLab (optical laboratory of the institute for human centered engineering) in cooperation with academic and industrial partners. The Spectralis Centaurus consists of an opto-mechanically upgraded diagnostic imaging platform (SPECTRALIS HRA+OCT, Heidelberg Engineering, Heidelberg, DE) together with an experimental SRT laser (MERILAS, Meridian, Thun, CH). The system utilizes OCT M-scans (motion-mode) for dosimetry control during treatment and takes advantage of all technologies that the SPECTRALIS platform already offers. Therefore, the device can be used for diagnosis of retinal diseases, intervention planning, SRT treatment, and follow-up examinations. The in house developed Centaurus treatment software (C++) is used for treatment planning on the fundus and implements the laser control.

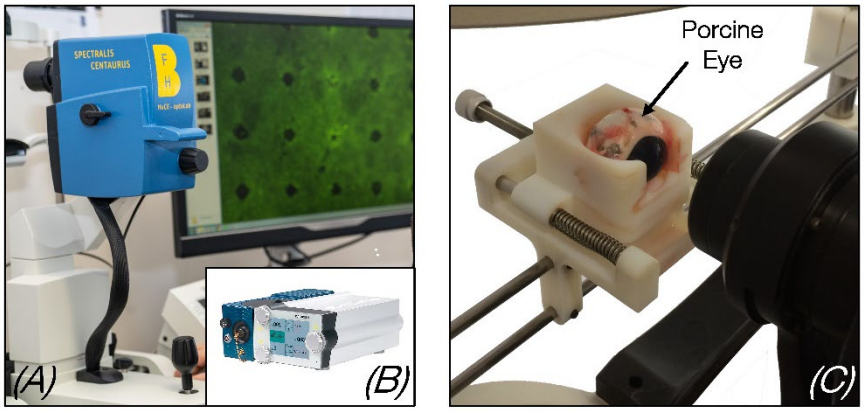

Figure 1. (A) Spectralis Centaurus system: upgraded diagnostic imaging platform (SPECTRALIS HRA+OCT, Heidelberg Engineering, Heidelberg, DE) together with the experimental SRT laser (MERILAS, Meridian, Thun, CH) (B) and placement of an ex-vivo porcine eye in front of the system (C)

The experimental SRT laser operates with pulses of 2 – 20 µs durations, emits at 532 nm, has a peak radiant power of 30 W and it delivers a variable repetition rate of 100 to 500 Hz. The optimized imaging system achieves a retinal top hat square of 120x120µm².

The OCT part of the Spectralis Centaurus is a spectral-domain, also called Fourier-domain, OCT system that allows high-speed and high-resolution imaging of the retina. The infrared beam of the super-luminescence diode of the OCT laser has an average wavelength of 870 nm with a bandwidth of 73 nm (840 nm – 913 nm). In the experiment presented here, OCT is used to observe signal variations in time-resolved sequences of A-scans, so called M-scans, which are correlated to the creation of RPE lesions. In total, 256 A-scans are recorder and stitched together to one M-scan, which leads to time resolved records of 7.76 ms duration by an A-scan rate of 33 kHz. The SRT laser was triggered to take place within this M-scan time slot. The recorded signal changes, so called fringe washouts, then allow to predict physiological lesions in the RPE.

Several ex-vivo porcine eye experiments were carried out to test the full parameter set of the experimental SRT laser and to investigate its selectivity. Experiments took place in mornings well within the common cellular survivability window

of five hours, within three hours post-mortem after extraction, from a local slaughter-house. During collection the porcine eyes were stored in normal saline. (9g NaCl/l). Before treatment, all superfluous muscles were surgically removed from the sclera.

As shown in Figure 5, for the experiment a treatment pattern with 19 laser photocoagulation (LPC) marker lesions was used. The marker lesions were applied by using the experimental SRT laser in CW-mode (200 ms pulse duration and 200 mW pulse power). The marker lesions served as orientation guide in the evaluation process after the treatment. Within the marker lesions, the SRT treatment pattern, with a dimension of 10 x 10 lesions, was located. The pulse duration was increased from top bottom (2 µs to 20), and the radiant energy was increases from left (20 µJ) to right (maximal 340 µJ at 20 µs). During the treatment, M-scans were recorded with the Spectralis Centaurus system.

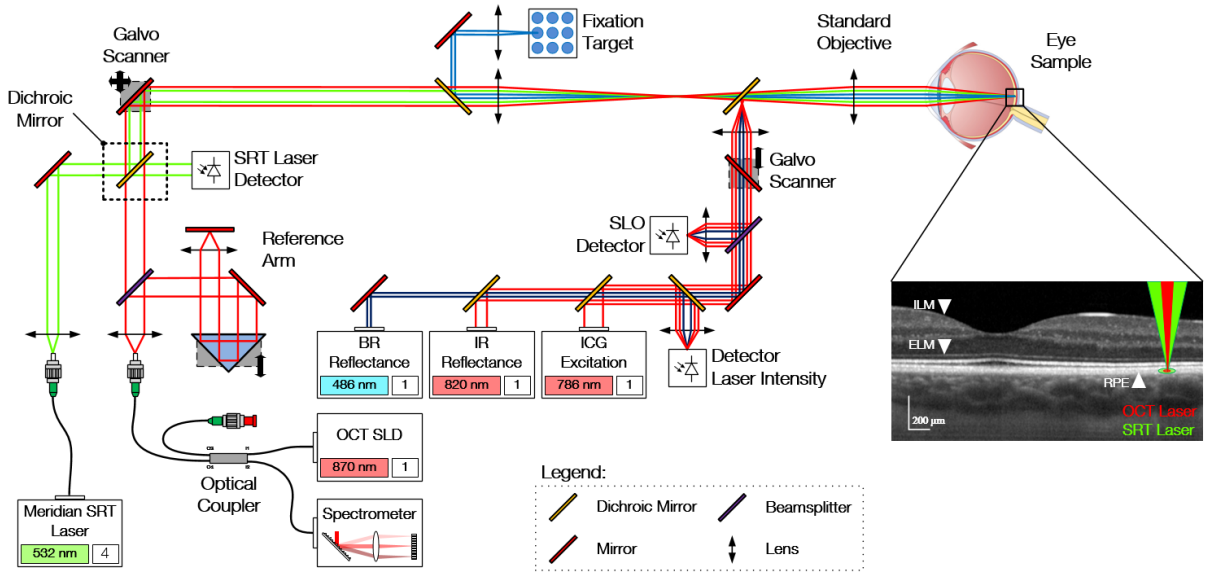

Figure 2. Setup and functionality of the Spectralis Centaurus system: The SRT and OCT laser beams are combined by a dichroic mirror (black-dashed rectangle). Retina scanning is performed by a galvo-scanner, a chromatically corrected objective focuses the collinear SRT and OCT laser beams. Reflected light is separately guided towards a spectrometer and a fast diode.

After SRT treatment, the porcine eyes were prepared for the staining and subsequent evaluation by fluorescence microscopy. The utilized two-color assay Live-Dead staining kit (L3224, Thermo Fisher Scientific, Waltham, MA, US) was used to determine vitality of RPE cells after SRT. Green-fluorescent calcein-AM (live) and red-fluorescent ethidium homodimer-1 (EthD-1, dead) indicate function or loss of plasma membrane integrity. The eyes were cut in half posterior to the lens, the vitreous body of the porcine eye was removed, and the treatment pattern had to be located by searching the LPC marker lesions. The LPC marker lesions appear as grayish spots on the retina and were always allocated in a rectangular grid. After localization, an area of approximately 10 x 10 mm, centered on the treatment pattern was cut free, stained and further washed in PBS. Evaluation took place under a fluorescence microscope (Axio Lab.A1, Carl Zeiss, Oberkochen, DE) and were documented by a camera (Gryphax Progres, Jenoptik, Jena, DE). Post-processing was performed with Fiji[21].

3. RESULTS

The experimental SRT laser's full range of available parameters was tested to verify SRT and OCT-controlled SRT feasibility. The ability to apply SRT lesions could be demonstrated for all pulse durations, ranging from 2 to 20 µs by applying single pulses. In Figure 3, the pulse duration is increased from top (2 µs) to bottom (20 µs), the radiant energy increases from left (20 µJ) to right (maximal 340 µJ at 20 µs). However, no SRT lesions were observed for pulses with 20 µJ radiant energy.

As depicted in Figure 3-B, averaged OCT B-scans can serve as a first tool to investigate the experimental SRT laser's selectivity. In total eight porcine eyes were treated. However, only five were evaluated with Live-Dead staining to get a

deeper insight into the relation between laser parameters and their impact on tissue. The full live-dead evaluation of a porcine RPE section is presented in Figure 5.

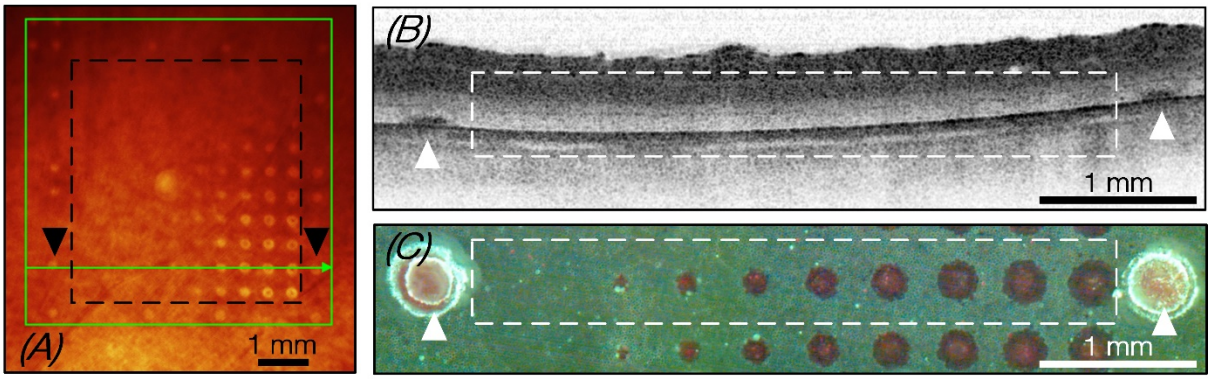

Figure 3. (A) IR fundus image of a porcine eye after SRT showing LPC marker lesions (e.g. black triangles) and SRT lesions in the SRT region (black-dashed rectangle) were the treatment pattern was applied. By analyzing line 9 (green arrow) of the treatment pattern in the IR fundus image (A), no retinal damage threshold can be documented in the corresponding OCT B-scan (B) by observing the SRT region (white-dashed rectangle) between the two LPC marker lesions (white triangles). By looking at the corresponding RPE layer (C) evaluated with live-dead staining, RPE lesions are highly present in the SRT region (white-dashed rectangle) between the two LPC marker lesions (white triangles). The presented section was treated with increasing pulse radiant energy from left to right (20 to 330 µJ) with a pulse duration of 18 µs.

As depicted in Figure 4, the Spectralis Centaurus system was able to observe signal variations in time-resolved sequences of A-scans (M-scans) which are correlated to the creation of RPE lesions. These findings were made for all pulse durations from 2 µs to 20 µs.

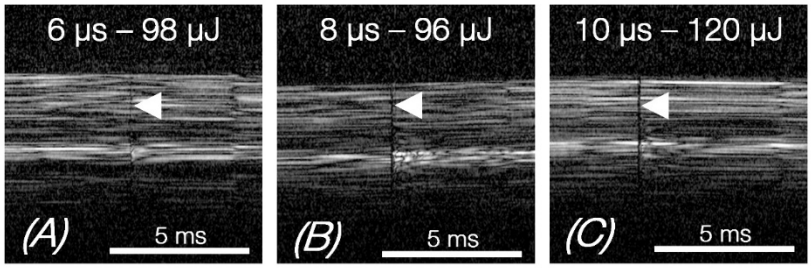

Figure 4. Selection of signal washouts for different pulse durations and radiant energies recorded with the Spectralis Centaurus system. It can be observed that the change of OCT signal strength can be different depending on pulse duration and radiant energy.

4. DISCUSSION

The experimental SRT laser was tested together with the Spectralis Centaurus system in multiple porcine sessions with the full extent of its parameters. The result of the experiments with different laser pulse durations correspond to the findings of similar studies. The results presented in Figure 3 suggest that the experimental SRT laser is selective for pulse durations up to 20 µs because no change in the tissue's structure due to strong heat dissipation can be observed compared to the LPC marker lesions. However, the pulse duration where thermal damage will take place is not clear defined jet. In general, laser irradiation should be delivered with a pulse duration shorter than the time needed for heat to diffuse toward surrounding tissue (thermal relaxation time).

The non-linear increase in lesion diameter with increasing energy observed in Figure 5 is thought to be the consequence of scattering in the upper retina layer and a slight defocusing on the curved retina.

With the current system a more detailed research is possible and implementing histology might be useful to investigate the boundary between microbubble effect and thermal coagulation effects. In-vivo experiments must show if irradiation with SRT pulse durations up to 20 µs induces anatomical changes or if such treatment is selective.

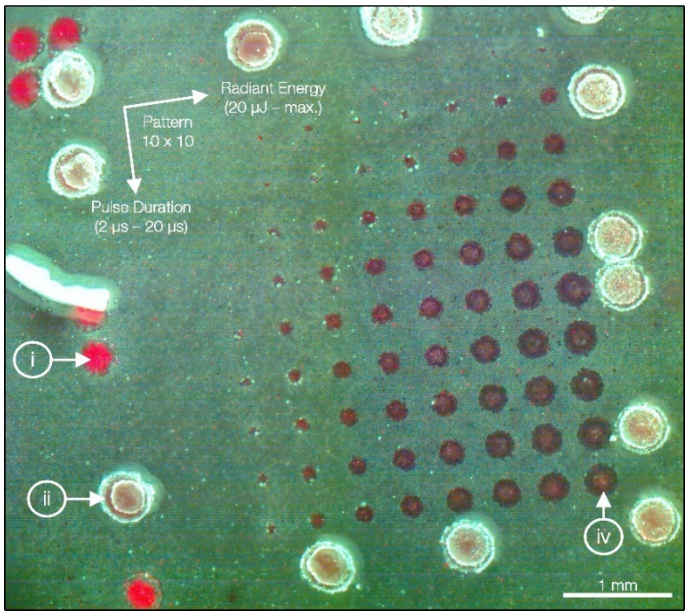

Figure 5. Depicted is the full extent of a live-dead evaluation of porcine RPE after SRT irradiation. The radiant energy was increased from left to right (20 to maximal 340 µJ by steps and the pulse duration from top to bottom (2 to 20 µs). It can be observed that marker lesions can occur as completely destroyed RPE (i) or with attached retinal tissue (ii) due to some kind of welding process, which is typically provoked by heat dissipation in LPC. The evaluation shows that the experimental SRT laser is able to create SRT lesions (iv) with its whole parameter set.

5. CONCLUSION AND OUTLOOK

For investigation of the clinical potential of OCT-controlled SRT, a system combining an opto-mechanically upgraded diagnostic imaging platform with an experimental green SRT laser was built. This Spectralis Centaurus system will allow accurate SRT treatment planning and energy dosing by leveraging high speed automated M-scan signal washout detection during ramping up the pulse energy. Being a multimodal system the Spectralis Centaurus system is not a sole treatment device but offers integrated diagnostic modalities that the preceding diagnostic imaging platform offered. This makes it a well-proven and reliable device for diagnosis, intervention planning, treatment and follow-up examination. It has the potential to promote SRT as the standard therapy for patients suffering from RPE-related retinal diseases. Nevertheless, further studies are ongoing to improve the safety of SRT with pulse durations up to 20 µs by confirming the exact therapeutic window and safety range.

6. ACKNOWLEDGEMENTS

We gratefully want to acknowledge the valuable support and the inspiring discussions with our colleague from the Medical Laser Center Lübeck: Veit Danicke, the colleagues from Meridian AG, Thun: Markus Stoller, Michael Stetter, Rudolf von Niederhäusern, Eric Odenheimer, the Heidelberg Engineering team: Ralf Kessler, Stefan Schmidt, Michael Reutter, Joerg Fischer, Tilman Otto and the colleagues from the Augenklinik, at the Inselspital Bern: Volker Enzmann, Anelia Schweri-Olac and Sebastian Wolf.

Founding: Swiss National Science Foundation, SNF grant #325230-141189; SNF grant #323523-163306 and Swiss Innovation Agency KTI 25030.1 PFLS-LS

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